Pharmacology of the Sympathetic Nervous System I

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Neurons of the ANS
Adrenergic Nerve Terminal

Neuronal (Uptake 1) vs Extraneuronal (Uptake 2)

Neuronal Uptake
Uptake 1
70-80%
Cocaine
TCA
MAO

Extraneuronal
Uptake 2
10-20%
COMT

Synthesis, action and fate of norepinephrine at neuroeffector sites
### MAO vs COMT

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<thead>
<tr>
<th>Location in cell</th>
<th>MAO</th>
<th>COMT</th>
</tr>
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<tbody>
<tr>
<td>Mitochondrial outer membrane</td>
<td>cytosol</td>
<td></td>
</tr>
<tr>
<td>Location in body</td>
<td>symp. nerve, placenta (MAO_A)</td>
<td>most tissues, not in sympath. nerve</td>
</tr>
<tr>
<td></td>
<td>platelets (MAO_B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>liver, kidney, brain (MAO_A + MAO_B)</td>
<td></td>
</tr>
</tbody>
</table>

**Effect of inhibition on NE levels**
- Increased NE level in symp. neuron, potentiates release by tyramine-like drugs
- Minor/no effect

### MAO vs COMT

**COMT**

![COMT Reaction]

- Inhibitors: Tolcapone, Pyrogallol
  - Parkinson’s D with L-Dopa
  - (rarely used, liver failure)

**MAO**

![MAO Reaction]

- Inhibitors: Non-selective
  - Depression: Tranylcypromine, Pargyline
  - Parkinson’s D: Selegiline

- Selective
  - Depression: MAO-A Clorgiline
  - MAO-B: Selegiline
Metabolism of Catecholamines

Metabolism by either MAO or COMT, inactivates drug

Major Metabolites
VMA
MOPEG

Adrenergic Agents – Relative Selectivity

<table>
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<tr>
<th>RECEPTOR</th>
<th>TISSUE</th>
<th>ACTIONS</th>
</tr>
</thead>
</table>
| **Alpha**<sub>1</sub> 
EPI > or = NE >> ISO | most vascular smooth muscle contraction, pupillary dilator muscle contraction (dilation), pilomotor smooth muscle contraction, vas deferens contraction, liver contraction, intestinal smooth muscle contraction, intestinal sphincters relaxation | 
| **Alpha**<sub>2</sub> 
NE > EPI >> ISO | some vascular smooth muscle contraction, nerve terminals (NE & Ach) aggregation, platelets inhibition of lipolysis, fat cells aggregation, inhibition of lipolysis | 
| **Beta**<sub>1</sub> 
ISO > EPI = NE | heart force, rate, conduction velocity dilation, coronary blood vessels dilatation, kidney renin release | 
| **Beta**<sub>2</sub> 
ISO > or = EPI >> NE | bronchial smooth muscle relaxation, uterine smooth muscle relaxation, intestinal smooth muscle relaxation, intestinal smooth muscle relaxation, vascular smooth muscle relaxation, liver relaxation, NA nerve terminals relaxation, fat cells lipolysis, | 
| **Beta**<sub>3</sub> 
ISO = NE > EPI | fat cells lipolysis |
### Second Messengers

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<tr>
<th>Receptor</th>
<th>Location</th>
<th>G Protein</th>
<th>2nd Messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1)</td>
<td>Effector tissues: smooth muscle, glands</td>
<td>Gq</td>
<td>(\uparrow\text{Ca}^{2+}, \uparrow\text{IP}_3, \text{DAG})</td>
</tr>
<tr>
<td>(\alpha_2)</td>
<td>Nerve endings, smooth smooth muscle</td>
<td>Gi</td>
<td>(\downarrow\text{cAMP})</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>Cardiac muscle, juxtaglomerular apparatus</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>(\beta_2)</td>
<td>Smooth muscle, lung</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>(\beta_3)</td>
<td>Adipose cells</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>(D_1, D_5)</td>
<td>Renal, vascular SM, brain</td>
<td>Gs</td>
<td>(\uparrow\text{cAMP})</td>
</tr>
<tr>
<td>(D_2, D_3, D_4)</td>
<td>Brain, cardiovascular</td>
<td>Gi</td>
<td>(\downarrow\text{cAMP})</td>
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### Phospholipase C

- **G-Protein coupled receptors**
  - Adrenergic Alpha1-receptors
  - Cholinergic
    - M1
    - M3
    - M5

- **Second Messenger**
  - \(\text{IP}_3, \text{DAG}\)

- **Effector tissues**: smooth muscle, glands
- **G-Protein coupled receptors**: Gq, Gi
- **2nd Messengers**: \(\text{Ca}^{2+}, \text{IP}_3, \text{DAG}\)

- **Vascular & Genitourinary**
  - Smooth muscle contraction
  - Aktivated protein kinase
  - Free calcium
  - Stored calcium

- **Sympathetic outflow causes release of NE at \(\alpha_1\)-receptors to cause Ca+ release and contraction of smooth muscle.**
Adenylate Cyclase

G-Protein coupled receptors

Stimulate
All Beta-receptors
D1, D5-receptors

Inhibit
Alpha2-receptors
D2, D3, D4-receptors
M2, M4-receptors

norepinephrine / epinephrine

IP3 / DAG

Ca++ / PKC

Ca++-dependent phosphorylase K.

phosphorylase a

glycogenolysis

↑ glucose-1-P

Hepatocyte

α1-AR

β2-AR

norepinephrine / epinephrine

IP3 / DAG

Ca++ / PKC

Ca++-dependent phosphorylase K.

phosphorylase a

glycogenolysis

↑ glucose-1-P

protein kinase A

phosphorylase kinase

phosphorylase a

glycogenolysis

Heart: Increased force of contraction, increased heart rate, increase AV nodal conduction velocity.
Catecholamines

A. Norepinephrine (limited use, pressor agent, shock)
   - Activates: both alpha, beta_1, beta_3, beta_2 (weakest)
   - Substrate for MAO & COMT, does not cross BBB

B. Epinephrine (DOC - Allergic reaction)
   - Activates both alpha, beta_1, beta_2, beta_3 (weakest)
   - Substrate for MAO & COMT, does not cross BBB

C. Dopamine (DOC – septic shock)
   - Precursor of NE and EPI
   - Activates dopamine- (low dose), beta_1- (moderate dose), alpha_1-receptors (high dose)
   - Substrate for MAO & COMT, does not cross BBB

D. Isoproterenol (asthma, cardiac stimulant)
   - Activates all beta receptors
   - Substrate for COMT, does not cross BBB
Non-Catecholamines – Beta agonists

- **Selective beta2-agonists:**
  - Albuterol, metaproterenol, salmeterol (LABA)
  - terbutaline, ritodrine

  Uses: asthma, premature labor

  Oral: Onset 1-2 hrs, duration 4-6 hrs
  Inhal: Onset 5-10 min, duration 3-4 hrs (fewer side effects)

- **Adverse effects:** cardiovascular (↑HR, ↓BP)

- **Selective beta1-agonists:**
  - Dobutamine, prenalterol

  Uses: Congestive heart failure
  Increase force, no change in HR or oxygen demand

Non-Catecholamines – Alpha agonists

- **Selective alpha1-agonists:**
  - Methoxamine, phenylephrine, metaraminol (direct & indirect actions, orally active)

  Uses: hypotension or shock, nasal decongestant

- **Selective alpha2-agonists:**
  - Clonidine, α-methyldopa (pro-drug), guanfacine

  Uses: chronic hypertension (CNS action)
  - opioid withdrawal (decrease severity)

  Side effects: impotence, dry mouth, rebound HT, sedation

  Dexmedetomidine: CNS action, 2A selectivity, iv for sedation/analgesia in surgery, less respiratory depression, increasing use. Caution: hypovolemic patient
  Tizanidine: CNS action to ↓muscle spasticity, CYP1A2
Adrenergic Nerve Terminal

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Tizanidine: CNS action to ↓ muscle spasticity, CYP1A2
**Alpha₂-Adrenoceptors**

CNS: hypotension, bradycardia, sedation, analgesia and ↓ muscle spasticity

Peripheral: ↓ salivation, ↓ secretion, ↓ bowel motility, contraction of vascular smooth muscle, diuresis

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**Dopamine Agonists**

- **Fenoldopam:**
  - D₁₆-agonist, no action on α1- or β-receptors
  - used for acute hypertension
  - iv short-term infusion (<48 hrs)
  - SE: ↑ ocular pressure, ↑ HR

- **Bromocriptine, Pramipexole:**
  - Parkinson’s Disease
  - Restless leg syndrome (RLS)
  - SE: drowsiness
Parkinson’s Disease

- General population 1:1000, over 60 1:75
- Tremor, stiffness, or clumsiness, usually involving one side, difficulty walking, fatigue, depression
- Progressive destruction of the dopaminergic nigrostriatal pathway
- Elevated cholinergic activity

**Treatment options:**
- MAO inhibitors:
- Dopamine agonists: bromocriptine, pramipexole
- L-Dopa
- Anticholinergics: benztropine
- Decarboxylase inhibitor: carbidopa
- COMT inhibition

**Indirectly-acting Sympathomimetics (displace transmitter)**

- **Amphetamine**, methamphetamine, methylphenidate
  - CNS stimulant, performance enhancer, physical & mental abuse
  - ↑alertness, mood, self-confidence, concentration, psychological dependence, tolerance, tachyphylaxis
- Uses: ADHD, appetite suppression (?), narcolepsy
- Toxicity: cardiovascular, restlessness, tremor, insomnia
- **Ephedrine (mixed)**
  - direct action (alpha- and beta-receptors)
  - indirect action to release norepinephrine
- Uses: nasal decongestant
- **Tyramine** (not a drug, interaction with MAO inhibitors)
Tachyphylaxis

1. Release of NE/DA from neurons
2. Inhibition of monoamine transmitter uptake
3. Binding to extracellular receptors
4. Inhibition of MAO

Amphetamine Action

1. Release of NE/DA from neurons
2. Inhibition of monoamine transmitter uptake
3. Binding to extracellular receptors
4. Inhibition of MAO
Indirectly-acting Sympathomimetics (cont.)

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Neuronal Uptake Inhibition

Inhibit neuronal uptake (Uptake1)
Can prevent the action of indirectly acting agents (e.g. amphetamine) and can potentiate the effects of NE (i.e. not removed from synaptic junction).

**Neuronal Uptake 1: 70-80%**

**Cocaine**

**Tricyclic antidepressants** (Imipramine, amitriptylline)
High dose: block alpha- & M-rec.

**Atomoxetine** (used for ADHD)

**Guanethidine** (competes for uptake)
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<td>(MAO&lt;sub&gt;A&lt;/sub&gt;) (MAO&lt;sub&gt;B&lt;/sub&gt;) (MAO&lt;sub&gt;A&lt;/sub&gt; + MAO&lt;sub&gt;B&lt;/sub&gt;)</td>
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<td>Effect of inhibition on NE levels</td>
<td>Increases NE level in symp. neuron, potentiates release by tyramine-like drugs</td>
<td>none/minor effect</td>
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<tr>
<td>Inhibitors</td>
<td>Pargyline, tranylcypromine (non-selective) Clorgyline (MAO&lt;sub&gt;A&lt;/sub&gt;-selective) Selegiline (MAO&lt;sub&gt;B&lt;/sub&gt;-selective)</td>
<td>Tolcapone, Entacapone, Pyrogallol</td>
</tr>
<tr>
<td>Clinical use of inhibitors</td>
<td>Depression (non-selective or MAO&lt;sub&gt;A&lt;/sub&gt;-selective) Parkinson’s disease (MAO&lt;sub&gt;B&lt;/sub&gt;-selective)</td>
<td>Parkinson’s D</td>
</tr>
<tr>
<td>Interactions</td>
<td>MAO inhibitors potentiate effects of tyramine (due mainly to blocking metabolism of tyramine by MAO in liver)</td>
<td>None, liver failure</td>
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### Parkinson’s Disease

- **General population**: 1:1000, over 60 1:75
- **Tremor, stiffness, or clumsiness**, usually involving one side, difficulty walking, fatigue, depression
- **Progressive destruction of the dopaminergic nigrostriatal pathway**
- **Elevated cholinergic activity**

**Treatment options:**
- **MAO inhibitors**:
- **Dopamine agonists**: bromocriptine pramiprexole
- **L-Dopa**
- **Decarboxylase inhibitor**: carbidopa
- **Anticholinergics**: benztrapine
- **COMT inhibition**

**Parkinsonian Brain:** 26% dopamine production compared with a healthy brain

**Dopamine agonists**

**Loss of intracellular dopamine due to absence of signal**

**Restoration of intracellular dopamine**

**KEY**

- ▲: Dopamine
- ▼: Dopamine agonist
Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

MAOI and Tyramine Crisis

↑Blood pressure, ↑Heart rate

Treatment: α-blocker or labetalol (α-, β-blocker)

Normally dietary tyramine is metabolized by MAO

With MAO inhibition, octopamine is produced and stored in vesicles with NE

Aged cheese, red wine are rich in tyramine
Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis ($\uparrow$BP, $\uparrow$HR)

Aged cheese & red wine are rich in tyramine

Therapeutic uses: Sympathomimetics 1

- **Asthma** (major use)
  - bronchodilation with $\downarrow$airway resistance
  - beta2-selective agents eg. albuterol

- **Allergic Reactions**
  - acute hypersensitivity reactions (food, bee sting, drug allergy)
  - epinephrine (DOC)

- **Nasal Decongestant** (common use)
  - vasoconstriction (ephedrine, phenylephrine)

- **Hypotension** (acute)
  - intoxication with antihypertensive agents, spinal anesthesia, hemorrhage
  - phenylephrine, methoxamine, **metaraminol**
Asthma

Albuterol
Terbutaline,
Metaproterenol
Salmeterol (LABA)

$\beta_2$-selective agonists
- bronchodilation

Inhalation vs oral
- less side effects

Ritodrine
- premature labor

Anaphylaxis

Epinephrine

- bronchodilation
- vasoconstriction
Therapeutic uses: Sympathomimetics 2

- **Hypertension**
  - Chronic: centrally acting $\alpha_2$-receptor agonists (clonidine, $\alpha$-methyl-dopa)
  - Acute: fenoldopam ($D_{1A}$-agonist)

- **Shock (Hypotension, need to treat cause)**
  - dopamine (DOC), epinephrine, NE
  - blood loss, cardiac failure, septic shock
  - ↓tissue perfusion, need to maintain BP, cerebral flow

- **Congestive Heart Failure: (acute)**
  - dobutamine, (dopamine)

- **Cardiac Heart Block & Cardiac Arrest**
  - epinephrine or isoproterenol

Therapeutic uses: Sympathomimetics 3

- **Parkinson’s Disease**
  - Inhibitors: MAO-B: selegiline, COMT: tolcapone
  - D-agonists: pramipexole Precursor: L-Dopa

- **Ophthalmic**
  - dilate the pupil (phenylephrine)
  - glaucoma (epinephrine)
  - also beta-blocking agents used (common)

- **Uterine Contraction**
  - suppress premature labor
  - ritodrine, terbutaline (not FDA approved)

- **Hyperactivity Disorder (ADHD)**
  - amphetamines, methylphenidate (ritalin)
  - NE uptake inhibition: atomoxetine

- **Others:** [obesity], narcolepsy: - amphetamines
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Toxic effects of Sympathomimetics

- Extensions of their receptor-mediated effects

- Cardiovascular (main)
  - cardiac stimulation ($\beta$-AR, arrhythmias)
  - hypertension ($\alpha$-AR, hemorrhage)

- CNS
  Especially those that cross BBB (ie. amphetamine)
  - restlessness
  - dizziness
  - insomnia

- Alpha2-receptor agonists
  - dry mouth, sedation, impotence